

19



Europäisches Patentamt
European Patent Office
Office européen des brevets

11 Publication number:

**0 264 129
A1**

12

EUROPEAN PATENT APPLICATION

21 Application number: **87115084.3**

51 Int. Cl.4: **C07C 149/36 , C07C 148/00**

22 Date of filing: **15.10.87**

30 Priority: **17.10.86 US 920813**

43 Date of publication of application:
20.04.88 Bulletin 88/16

84 Designated Contracting States:
AT BE CH DE ES FR GB GR IT LI LU NL SE

71 Applicant: **MERRELL DOW
PHARMACEUTICALS INC.
2110 E. Galbraith Road
Cincinnati Ohio 45215(US)**

72 Inventor: **Krauss, Richard C.
4308 Congress Drive
Midland Michigan 48640(US)**

74 Representative: **Macchetta, Francesco et al
Gruppo Lepetit S.p.A. Patent and Trademark
Department 34, Via Roberto Lepetit
I-21040 Gerenzano (Varese)(IT)**

54 **Process for preparing 2,6-ditertiarybutyl-4-mercaptophenol.**

57 In a process for making 2,6-di-tertiarybutyl-4-mercaptophenol by the Zn/acid reduction of bis (3,5-di-tertiarybutyl-4-hydroxyphenyl)polysulfide the addition of catalytic amounts of lead to the zinc reagent results in substantial improvement in the process.

EP 0 264 129 A1

PROCESS FOR PREPARING 2,6-DI-TERTIARYBUTYL-4-MERCAPTOPHENOL**BACKGROUND OF INVENTION****FIELD OF THE INVENTION**

5

This invention relates to a novel improvement in the process of preparing 2,6-di-tertiarybutyl-4-mercaptophenol by a zinc-acid reduction of bis(3,5-di-tertiarybutyl-4-hydroxyphenyl)polysulfide in the presence of a catalytic amount of lead. The addition of catalytic amounts of lead to the zinc reagent increases the reduction efficiency of the above reaction. The above process represents an intermediate step for making 4,4'-isopropylidenedithio-bis-(2,6-di-tertiarybutylphenol), which has been described in U.S. Patent 3,576,883 as an effective pharmaceutical agent for the reduction of serum cholesterol and has been approved for marketing in the United States by the Food and Drug Administration (FDA).

10

DESCRIPTION OF PRIOR ART

15

The reduction of bis(3,5-di-tertiarybutyl-4-hydroxyphenyl)polysulfide in the presence of zinc/HCl is disclosed in U.S. Patent 3,952,064 and 3,479,407 and in Japanese Patent Application 73-28425. No mention, however, is made of the utility of a catalytic amount of lead in this reaction. U.S. Patent 3,479,407 discloses the preparation of bis(3,5-di-tertiarybutyl-4-hydroxyphenyl)polysulfide by sulfurization of 2,6-di-tertiarybutylphenol with sulfur monochloride in the presence of an iodine catalyst. The Polysulfide can then be reduced to the corresponding mercaptophenol, i.e., 2,6-di-tertiarybutyl-4-mercaptophenol, which can be condensed using acetone under acidic conditions to form 4,4'-iso-propylidenedithio-bis-(2,6-di-tertiarybutylphenol), as described in U.S. Patent 3,576,883. This reaction sequence is as follows:

25

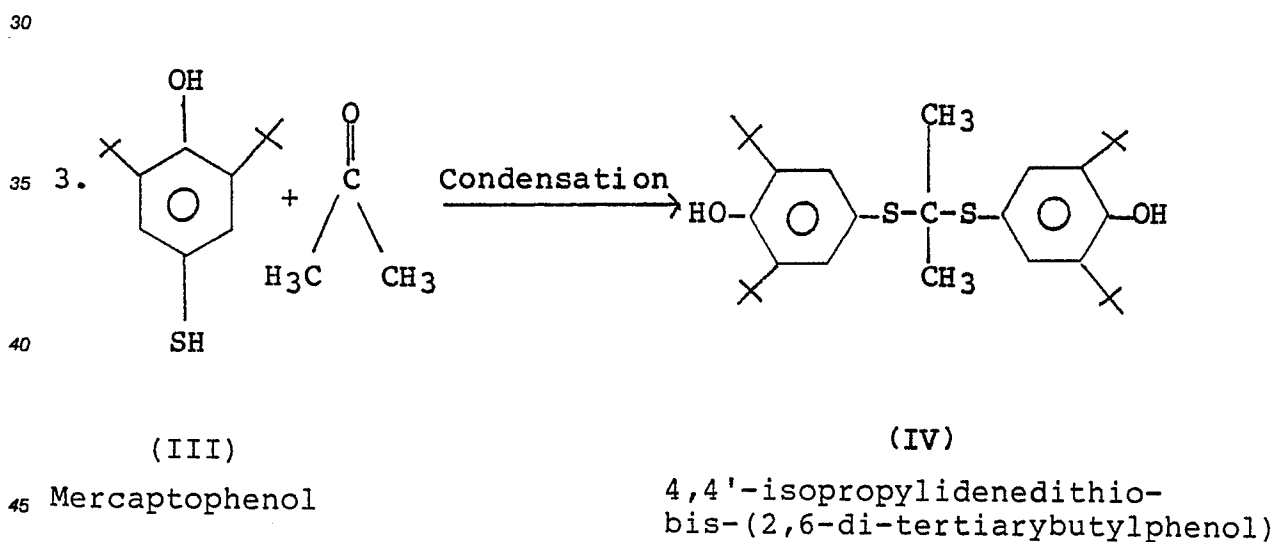
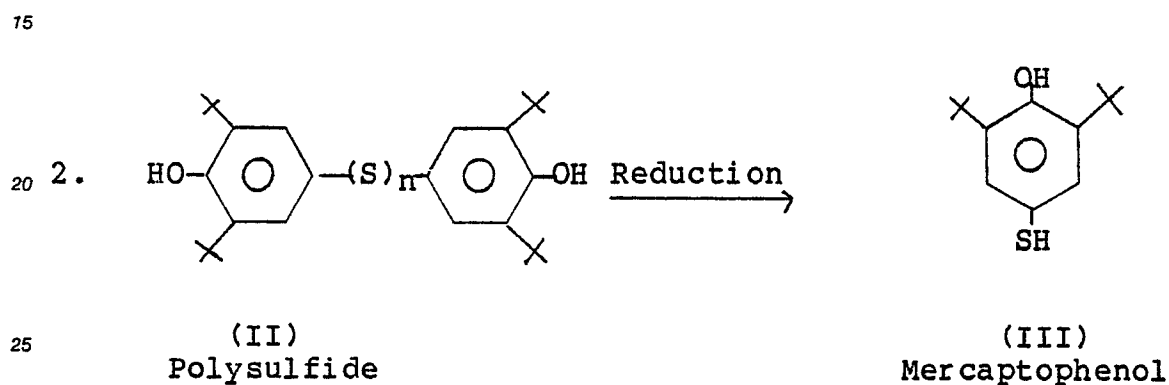
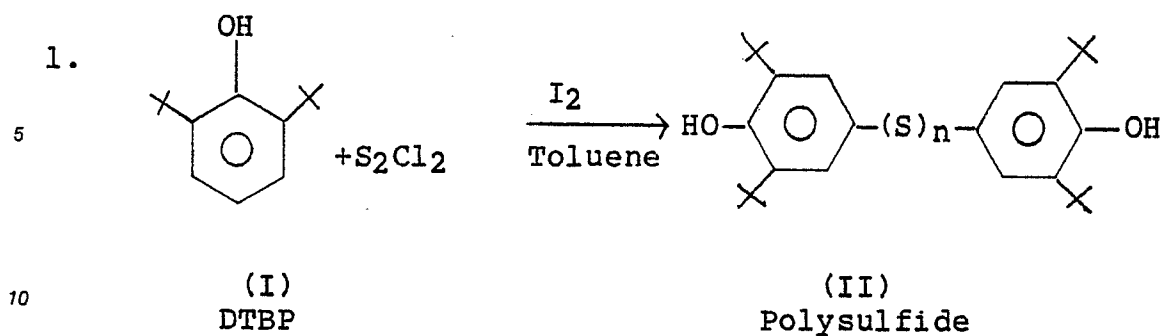
30


35

40

45

50



 = tertiarybutyl group

$n = 2, 3, 4, \dots$; principal product is the disulfide

The Zn/HCl reduction of the Polysulfide (II) to the corresponding Mercaptophenol (III) is inconsistent, resulting in variable, incomplete reductions which require multiple cycles through the reductive step to obtain satisfactory yields. The present invention which comprises an improvement in this process results in consistent high-yield reductions of the Polysulfide (II) to the corresponding Mercaptophenol (III) and substantially improves the process of making 4,4'-isopropylidenedithio-bis-(2,6-di-tert-butylphenol).

SUMMARY OF THE INVENTION

The following terms are used herein as follows:

"DTBP" refers to as 2,6-di-tertiarybutylphenol (I).

5 "Polysulfide" and "Bis(3,5-di-tertiarybutyl-4-hydroxyphenyl)polysulfide" both are used to refer to one or more species of bis(3,5-di-tertiarybutyl-4-hydroxyphenyl)polysulfide (II) including the di-, tri-, tetra-, and other higher order sulfides, and including single species as well as mixtures thereof. Typically, the Polysulfide is a mixture of two or more species with the disulfide present in amounts greater than other species.

10 "Mercaptophenol" refers to 2,6-di-tertiarybutyl-4-mercaptophenol (III).

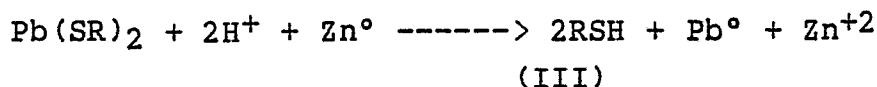
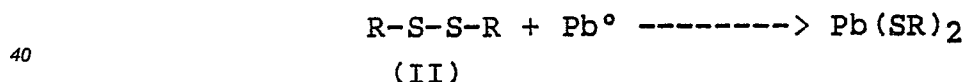
The novel improvement in the process of the Zn/acid reduction of Polysulfide (II) to Mercaptophenol (III) comprises the addition of a catalytic amount of lead to the zinc reagent in order to provide a consistent high-yield reduction.

In general, zinc reagent is contacted with a catalytic amount of lead, i.e., an amount which is sufficient
15 to provide a substantial increase in yield of Mercaptophenol (III) or a substantial decrease in the reaction time required for the reduction of Polysulfide (II) in comparison to that obtained with zinc reagent in the absence of that amount of added lead. Preferably, an aqueous slurry of zinc dust is agitated with sufficient $PbCl_2$, or other soluble lead salt such as lead acetate, to provide from about 1200 to about 5000 parts by weight of lead per million parts by weight of zinc and more preferably to provide from about 2700 to about
20 3300 parts by weight of lead per million parts by weight of zinc. This aqueous slurry of zinc dust and soluble lead salt is preferably agitated at ambient temperature for about 0.5 to about 1.0 hour in the presence of Polysulfide (II). The reduction of Polysulfide (II) to Mercaptophenol (III) is initiated with the addition of acid, preferably HCl, to this mixture. Other solvents, such as acetic acid, which are capable of supporting lead and zinc ion and are compatible with an acid-mediated reduction of the Polysulfide (II) can
25 also be used. Although the above order of mixing the reactants is preferred, i.e., the addition of acid last to initiate the reaction, it is understood that other orders of addition of the reactants are encompassed by the present invention. In addition, zinc can be pre-treated with appropriate amounts of lead and stored for future use.

It is likely that the contacting of the zinc catalyst with lead ion results in the reduction of the lead ion to
30 elemental lead and the consequent deposition of lead on the surface of the zinc. This is described by the following reaction scheme:



The mechanism for the Zn/acid reduction of the Polysulfide (II) to Mercaptophenol (III) in the presence
35 of a catalytic amount of lead is thought to involve the following sequence in which lead cleaves the disulfide bond of the Polysulfide (II) in an initial step followed by an electrochemical reduction of the lead mercaptide salt to give the Mercaptophenol (III).



45 The present invention, however, is understood not to be limited by any particular theory of mechanism in bringing about the improvement in the process of preparing the Mercaptophenol (III).

The following examples illustrate that the addition of lead to zinc catalyst in amounts sufficient to provide a final concentration of about 1100 ppm to about 7000 ppm of lead, results in substantial
50 improvement in product yield in the Zn/acid reduction of Polysulfide (II) to Mercaptophenol (III).

55

Example 1

In a series of runs, a Zn/HCl reduction of Polysulfide (II) to Mercaptophenol (III) was carried out with a zinc reagent in the presence and absence of various amounts of added lead.

5 A 250 milliliter (ml) flask was charged with 12.2 grams (0.187 moles) of zinc (which had been analyzed and found to contain about 140 parts per million of lead) and 100 ml of sulfurization mixture which contained Polysulfide (II) formed by reacting 0.25 moles of DTBP (I) with sulfur monochloride in the presence of an iodine catalyst. 32 ml of water and 32 ml of 37% HCl were added and the reaction mixture was heated over about 10 minutes to about 70°C and held. The reductions were run until no more product
10 was being formed, generally 200 to 250 minutes.

This reaction was repeated with the addition of lead to the zinc reagent as follows: A 250 ml flask was charged with 12.2 grams (0.187 moles) of the same zinc as above (containing about 140 ppm of lead), 100 ml of sulfurization mixture from 0.25 moles of DTBP, and 32 ml of a PbCl₂ solution in water. The amount of PbCl₂ was varied in different runs to provide a final lead concentration of from about 1100 to about 6200
15 parts of lead per million parts of zinc. The mixture was agitated for 1 hour at 25°C before adding 32 ml of 37% HCl and heating as described above.

As shown in Table 1, the reduction results in a 33% yield in the absence of added lead, whereas the addition of lead to the zinc reagent to provide a total of 1100 to 6200 ppm of lead results in a 79 to 88% yield. These results demonstrate that the addition of catalytic amounts of lead to the zinc reagent provides
20 a substantial increase in the yield of the reduction product over that found with the zinc reagent in the absence of added lead.

TABLE 1

Results of Zn/HCl Reduction
With and Without the Addition of Lead

Run	Added Pb (ppm)	% Yield
1 (Control)	0	33
2	1100	79
3	2900	87
4	6200	88

Example 2

In another experiment, the time course of the reduction was followed using a zinc reagent in the presence and absence of added lead.

45 A 1-liter flask was charged with 83 grams (1.27 moles) of zinc (which was analyzed and found to contain about 200 ppm of lead), 100 ml of water, and 407 grams of water-washed sulfurization mixture containing Polysulfide (II). The slurry was warmed to 78°C and 332 grams of 37% hydrochloric acid was added over the course of about 30 minutes while maintaining constant stirring. The disappearance of the Polysulfide (II) during the reaction was monitored by measuring the peak area of the disulfide as analyzed
50 by HPLC (High Pressure Liquid Chromatography) in samples of the reaction mixture taken at various times during the reaction.

This reaction was then repeated with the addition of lead to the zinc reagent as follows: A 1-liter flask was charged with 83 grams (1.27 moles) of the same zinc as above (containing about 200 ppm of lead), 100 ml of water, 0.196 grams (0.704 mmoles) of PbCl₂, and 407 grams of water-washed sulfurization
55 mixture containing Polysulfide (II). The resulting slurry was agitated at ambient temperature for about 30 minutes before addition of 332 grams of 37% HCl and monitored as described above. This zinc reagent was treated with a quantity of PbCl₂ calculated to provide a final lead concentration of about 2000 parts by weight of lead per million parts by weight of zinc.

As shown in Table 2, the zinc to which no lead had been added (about 200 ppm of lead) provided a 7% decrease in the Polysulfide (II) after 115 minutes of reaction time (Run 1), whereas the zinc to which lead had been added (about 2000 ppm of lead) provided a 74% decrease by 90 minutes and essentially complete disappearance of Polysulfide (II) by 150 minutes (Run 2). These results demonstrate that the addition of lead to a zinc reagent provides a substantial improvement in the reaction time required for reduction of Polysulfide (II) to the Mercaptophenol (III) product.

TABLE 2
Time Course of Zn/HCl Reduction
With and Without the Addition of Lead
% Decrease in Polysulfide (II)*

Reaction Time	Run 1	Run 2
<u>Minute</u>	<u>(No Added Pb)</u>	<u>(Added Pb)</u>
0	0.0	0.0
13	3.0	0.0
26	3.1	9.0
43	---	28.0
44	6.0	----
90	---	74.0
115	7.0	----
150	---	97.0

*The decrease in Polysulfide (II) is measured as a % decrease in HPLC peak area of the disulfide peak per mg of reaction mixture. The disulfide is the most abundant and difficult of the Polysulfides (II) to reduce; its peak area as a function of reaction time is a measure of the degree and efficiency of this reduction.

It is understood that the foregoing detailed description is given merely by way of illustration and that many modifications may be made therein without departing from the spirit or scope of the present invention.

Claims

1. In a process for making 2,6-di-tertiarybutyl-4-mercaptophenol by reduction of a bis(3,5-di-tertiarybutyl-4-hydroxyphenyl)polysulfide in the presence of zinc and acid, the improvement which comprises contacting the zinc with a catalytic amount of lead.

2. Process of claim 1 wherein the reaction mixture contains from about 1200 to about 5000 parts by weight of lead per million parts by weight of zinc.

3. Process of claim 1 wherein the reaction mixture contains from about 2700 to about 3300 parts by weight of lead per million parts by weight of zinc.

4. In a process for making 2,6-di-tertiarybutyl-4-mercaptophenol by sulfurization of 2,6-di-tertiarybutylphenol and reduction of the sulfurization product in the presence of zinc and acid, the improvement which comprises contacting the zinc with a catalytic amount of lead.

5. Process of claim 4 wherein the reaction mixture contains from about 1200 to about 5000 parts by weight of lead per million parts by weight of zinc.

6. Process of claim 4 wherein the reaction mixture contains from about 2700 to about 3300 parts by weight of lead per million parts by weight of zinc.

7. In a process for making 4,4'-isopropylidenedithio-bis-(2,6-di-tertiarybutylphenol) by reduction of a bis-(3,5-di-tertiarybutyl-4-hydroxyphenyl)polysulfide in the presence of zinc and acid, and reacting the reduction product with acetone under acidic conditions, the improvement which comprises contacting the zinc with a catalytic amount of lead.
- 5 8. Process of claim 7 wherein the reaction mixture contains from about 1200 to about 5000 parts by weight of lead per million parts by weight of total zinc.
9. Process of claim 7 wherein the reaction mixture contains from about 2700 to about 3300 parts by weight of lead per million parts by weight of zinc.
- 10 10. In a process for making 2,6-di-tertiarybutyl-4-mercaptophenol by reduction of a bis(3,5-di-tertiarybutyl-4-hydroxyphenyl)polysulfide in the presence of zinc and acid, the improvement which comprises conducting the reduction in the presence of a catalytic amount of lead.
11. Process of claim 10 wherein the reaction mixture contains from about 1200 to about 5000 parts by weight of lead per million parts by weight of zinc.
12. Process of claim 10 wherein the reaction mixture contains from about 2700 to about 3300 parts by weight of lead per million parts by weight of zinc.
- 15 13. In a process for making 2,6-di-tertiarybutyl-4-mercaptophenol by sulfurization of 2,6-di-tertiarybutylphenol and reduction of the sulfurization product in the presence of zinc and acid, the improvement which comprises conducting said reduction in the presence of a catalytic amount of lead.
14. Process of the reduction step of claim 13 wherein the reaction mixture contains from about 1200 to about 5000 parts by weight of lead per million parts by weight of zinc.
- 20 15. Process of the reduction step of claim 13 wherein the reaction mixture contains from about 2700 to about 3300 parts by weight of lead per million parts by weight of zinc.
16. In a process for making 4,4'-isopropylidenedithio-bis-(2,6-di-tertiarybutylphenol) by reduction of a bis(3,5-di-tertiarybutyl-4-hydroxyphenyl)polysulfide in the presence of zinc and acid, and reacting the reduction product with acetone under acidic conditions, the improvement which comprises conducting said reduction in the presence of a catalytic amount of lead.
- 25 17. Process of claim 16 wherein the reaction mixture contains from about 1200 to about 5000 parts by weight of lead per million parts by weight of zinc.
18. Process of claim 16 wherein the reaction mixture contains from about 2700 to about 3300 parts by weight of lead per million parts by weight of zinc.
- 30

35

40

45

50

55



DOCUMENTS CONSIDERED TO BE RELEVANT			EP 87115084.3
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,A	<u>US - A - 3 479 407</u> (ROBERT J. LAUFER) * Column 2, line 12 - column 3, line 14; column 4, lines 1-22 * --	1,4,10,13	C 07 C 149/36 C 07 C 148/00
D,A	<u>US - A - 3 952 064</u> (WILLIAM G. WHALLEY) * Claims 1,13; column 5, lines 10-36 * --	1,4,10,13	
A	<u>US - A - 3 129 262</u> (ROBERT J. LAUFER) * Example 11 * --	1,4,10,13	
A	<u>US - A - 3 275 694</u> (WILLI HAHN et al.) * Claims 1,7; column 4, lines 4-19 * --	1,4,10,13	TECHNICAL FIELDS SEARCHED (Int. Cl.4) C 07 C 149/00 C 07 C 148/00
D,A	<u>US - A - 3 576 883</u> (MARTIN B. NEVWORTH) * Claim 4; column 2, lines 20-50; example 6 * ----	1,7,16	
The present search report has been drawn up for all claims			
Place of search VIENNA		Date of completion of the search 15-12-1987	Examiner REIF
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	